Sleep Medicine 15 (2014) 1405–1410

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

# Sleep disorders increase the risk of burning mouth syndrome: a retrospective population-based cohort study

Chun-Feng Lee [a,b], Kuan-Yu Lin [c], Ming-Chia Lin [d], Cheng-Li Lin [e], Shih-Ni Chang [f], Chia-Hung Kao [g,h,*]

[a] Department of Oral and Maxillofacial Surgery, Buddhist Tzu Chi General Hospital, Taichung Branch, Taichung, Taiwan
[b] Department of Dental Laboratory Technology, Shu-Zen Junior College of Medicine and Management, Kaoshiung, Taiwan
[c] Department of Nursing, Central Taiwan University of Science and Technology, Taichung, Taiwan
[d] Department of Nuclear Medicine, E-DA Hospital, Kaohsiung, Taiwan
[e] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[f] Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
[g] Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, Taichung, Taiwan
[h] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

*Article history:*
Received 15 March 2014
Received in revised form 22 June 2014
Accepted 27 June 2014
Available online 23 July 2014

*Keywords:*
Burning mouth syndrome (BMS)
Comorbidity
Sleep disorder (SD)
National Health Insurance
Retrospective cohort study

ABSTRACT

*Background:* Sleep disorders (SD), including apnea and nonapnea, and burning mouth syndrome (BMS) have been mutually associated with systemic diseases. Based on our research, the association between BMS and SD has not been elucidated. We determined whether SD patients have an increased risk of BMS.
*Methods:* We used information from health insurance claims obtained from the Taiwanese National Health Insurance (NHI) program. We identified patients newly diagnosed with sleep apnea syndrome between 1998 and 2001 as the apnea SD cohort, and newly diagnosed patients with nonapnea SD as the nonapnea SD cohort. The non-SD cohort was 1:2 frequency matched the case group according to sex, age, and index year. We analyzed the risks of BMS by using Cox proportional hazards regression models.
*Results:* Compared with the non-SD cohort, both of the apnea SD (adjusted HR = 2.56, 95% CI = 1.30–5.05) and nonapnea SD (adjusted HR = 2.89, 95% CI = 2.51–3.34) were associated with a significantly higher risk of BMS. The hazard ratio (HR) increased with increased age in the apnea SD cohort and in the nonapnea SD cohort compared with patients younger than 40 years of age. Female apnea SD patients (IRR = 4.63, 95% CI = 3.82–5.61) had a higher risk of developing BMS than did male patients (IRR = 1.76, 95% CI = 1.39–2.24).
*Conclusions:* Based on our research, SD might increase the risk of BMS.


## 1. Introduction

Sleep disorders (SD) have affected approximately 4–6 million people in Taiwan according to a survey by the Taiwan Society of Sleep Medicine (TSSM) [1]. Sleep is a critical factor for maintaining mental and physical health [2]. Lack of sleep and sleep deprivation threatens a person's health. The primary effects of sleep deprivation include physical effects, such as sleepiness, chronic fatigue syndrome, hypertension, cognitive disorder (eg, deteriorated attention and motivation, diminished concentration and intellectual capacity, and increased risk of accidents during working and driving), and mental health problems [3]. SD impairs the ability to think, manage stress, and maintain a healthy immune system and emotions. Complete sleep deprivation has been fatal in certain animal study models [4]. It is implicated that sleep is a crucial and essential factor of quality of life. Recent studies have shown an association between the immune system and SD [5–7]. The mechanisms by which SD affect health are unclear. However, certain recent studies indicated that SD might also affect or aggravate chronic pain and pain sensation by producing a hyperalgesic state in healthy people, which influences pain perception [8]. The relationship between SD and pain is very complex and the possible mechanism might be sleep and pain are both processed via the high pathway of the central nervous system (CNS) and through a pain–sleep interaction mechanism [9]. Clinically, pain can directly affect the sleep quality and quantity of patients with pain related to their underlying medical diseases, such as fibromyalgia, rheumatoid arthritis, and cancers [10,11] and psychiatric disorders such as anxiety and depression [9,12].

Chun-Feng Lee and Ming-Chia Lin are contributed equally for this work.
* Corresponding author at: Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan. No. 2, Yuh-Der Road, Taichung 404, Taiwan. Tel.: +886-4-22052121, ext. 7412; fax: +886-4-22336174.
*E-mail address:* d10040@mail.cmuh.org.tw (C-H. Kao).

http://dx.doi.org/10.1016/j.sleep.2014.06.009
1389-9457/

Burning mouth syndrome (BMS) is an idiopathic, chronic pain condition that affects large populations in modern society, characterized by a burning, stinging, and itching sensation of oral mucosa in the absence of any organic disease [13,14]. BMS is also defined by the International Association for the Study of Pain [15] as a burning pain in the oral mucous membrane and tongue, with normal signs and laboratory data lasting 4–6 months [16,17]. Butlin and Oppentheim first described it as glossodynia [18]; however, it is currently referred to as glossopyrosis, oral dysesthesia, sore tongue, stomatodynia, stomatopyrosis, and most commonly as BMS. The BMS mechanism is not fully elucidated at present, but the neuropathic mechanism for BMS is currently acceptable [19]. Studies have revealed trigeminal nerve alterations in both hyper- and hyposensitivity as well as fiber neuropathy [19–21]. BMS is also associated with a high prevalence of psychiatric symptoms or mental disorders [22,23]. Therefore, the pathogenesis mechanism remains to be determined. Previous studies have reported sleep dysfunction as a risk factor of patients with BMS [12,24]. However, no large population-based study has outlined the relationship between BMS and SD in Taiwan. Thus, we investigated whether SD, which includes nonapnea SD and apnea SD (or obstructive sleep apnea disorder), increases the risk of BMS. The original database was derived from the Taiwanese National Health Insurance (NHI) system in Taiwan. The results presented in this paper were derived from a retrospective cohort study to assess the possibility of a lower risk of BMS with clinical management of apnea and nonapnea SD.

## 2. Materials and methods

### 2.1. Data sources

In March 1995, the Taiwanese government implemented the National Health Insurance (NHI) program, which provides universal health insurance coverage to 99% of the population of Taiwan. The National Health Research Institutes (NHRI) compiles all inpatient and outpatient medical-benefit claims in the NHI program and releases the database for research purposes. The National Health Insurance Research Database (NHIRD) contains medical information, including inpatient and outpatient care facilities, drug prescriptions, insurant sex, date of birth, date of visit or hospitalization, and diagnoses coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. Previous studies have described the details of the NHIRD. We analyzed the one million beneficiaries randomly selected from all insurants from 1996 to 2000, which has been demonstrated to be representative of the entire population. The study conformed to STROBE Guidelines. The NHRID encrypts the patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient's sex, date of birth, registry of medical services, and medication prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101-012).

### 2.2. Study participants

For the case cohorts, we identified patients newly diagnosed with sleep apnea syndrome (ICD-9-CM 780.51, 780.53, and 780.57) between 1998 and 2001 as the apnea-SD cohort, and patients newly diagnosed with nonapnea SD (ICD-9-CM 307.4 and 780.5, except 780.51, 780.53, and 780.57) as the nonapnea-SD cohort. Patients were excluded if they were younger than 20 years of age or were diagnosed with BMS (ICD-9-CM 781.1, 529.0, and 529.6) before the index date. In total, 47,941 patients with SD comprised the case group. The same exclusion criteria were also applied to the non-SD control. The non-SD cohort was 1:2 frequency matched to the case group by sex, age, and index year ($n$ = 95 882). We excluded patients with medication history of angiotensin-converting enzyme (ACE) inhibitors. Finally, there were a total of 39,349 subjects in the SD cohort and 86,299 subjects in the non-SD cohort.

### 2.3. Outcome measurement and comorbidities

The index date for each participant was the first SD diagnosis date. We identified the study endpoint as the first diagnosis of BMS from outpatient claims or hospitalization records from 1998 to 2010. All of the study participants were followed from the index date to endpoint occurrence, withdrawal from the database, or the end of 2010, whichever date came first.

We also incorporated inpatient and outpatient diagnosis records to ascertain the baseline comorbidities, including diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), dementia (ICD-9-CM 290.0–290.4, and 331.0), parkinsonism (ICD-9-CM 332), trigeminal neuralgia (ICD-9-CM 350.1), temporomandibular joint disorder (ICD-9-CM 524.6), anxiety (ICD-9-CM 300.00), and depression (ICD-9-CM 296.2–296.3, 300.4, 311).

### 2.4. Statistical analysis

We compared the baseline characteristics between apnea SD, nonapnea SD, and non-SD controls by using the chi-square test. The age- and sex-specific incidence densities (IDs) were determined under the Poisson assumption. Cox proportional hazards regression models were performed with adjustment for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, dementia, parkinsonism, trigeminal neuralgia, temporomandibular joint disorders, anxiety and depression. For estimating the cumulative incidence of BMS in SD patients and non-SD patients, we performed a survival analysis by using the Kaplan–Meier method, with significance based on the log-rank test. All statistical analyses were performed using SAS (Version 9.2; SAS Institute, Cary, NC, USA). Statistical significance was determined by a data type I error of 0.05.

## 3. Results

Table 1 presents the baseline characteristics of the patients in the three groups. The distribution of age varied somewhat different, but significant. Approximately half of the study participants were 41–65 years of age. The mean ages of the SD cohort and non-SD cohort were 49.8 (±15.6) and 50.6 (±15.8) years, respectively. In the apnea SD cohort, most patients were men (62.0%), which inverted in the nonapnea SD cohort (36.0%). Patients in the nonapnea SD cohort were likely to have diabetes (5.64%, $P < 0.001$), dementia (0.39%, $P < 0.001$), parkinsonism (1.01%, $P < 0.001$), anxiety (3.99%, $P < 0.001$), and depression (6.17%, $P < 0.001$), whereas the apnea SD cohort patients were likely to have hypertension (27.4%, $P < 0.0001$), hyperlipidemia (21.5%, $P < 0.0001$), trigeminal neuralgia (0.27%, $P < 0.0001$), and temporomandibular joint disorders (0.54%, $P < 0.0001$).

Compared with the non-SD cohort, the apnea SD (IRR = 2.84, 95% CI = 2.45–3.30; adjusted HR = 2.56, 95% CI = 1.30–5.05) and nonapnea SD (IRR = 3.07, 95% CI = 2.95–3.19; adjusted HR = 2.89, 95% CI = 2.51–3.34) were associated with a significantly higher risk of BMS (Table 2). Figure 1 presents the cumulative incidence of BMS compared with the apnea SD cohort and the nonapnea SD cohort. The risk of BMS was significantly higher for patients both in the apnea SD cohort (log-rank $P = 0.001$) and the nonapnea SD cohort (log-rank $P < 0.001$) than for participants without SD.

Female apnea SD patients (IRR = 4.63, 95% CI = 3.82–5.61) had a higher risk of developing BMS than did male patients (IRR = 1.76,

**Table 1**
Comparison of demographics and comorbidity between SD patients and controls.

| | Sleep disorder | | | | | | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | Apnea SD (*N* = 744) | | Non-apnea SD (*N* = 38,605) | | Total (*N* = 39349) | | Control (*N* = 86299) | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | |
| Age, year | | | | | | | | | <0.001 |
| ≤40 | 245 | 32.9 | 11,435 | 29.6 | 11,680 | 29.7 | 23,780 | 27.6 | |
| 41–65 | 393 | 52.8 | 19,530 | 50.6 | 19,923 | 50.6 | 43,912 | 50.9 | |
| >65 | 106 | 14.3 | 7640 | 19.8 | 7746 | 19.7 | 18,607 | 21.6 | |
| Mean (SD) | 47.6 | 14.2 | 49.8 | 15.6 | 49.8 | 15.6 | 50.6 | 15.8 | <0.001[a] |
| Sex | | | | | | | | | 0.11 |
| Female | 283 | 38.0 | 24,722 | 64.0 | 25,005 | 63.6 | 54,435 | 63.1 | |
| Male | 461 | 62.0 | 13,883 | 36.0 | 14,344 | 36.5 | 31,864 | 36.9 | |
| Comorbidity | | | | | | | | | |
| Diabetes | 38 | 5.11 | 2176 | 5.64 | 2214 | 5.63 | 3018 | 3.50 | <0.001 |
| Hypertension | 204 | 27.4 | 9786 | 25.4 | 9990 | 25.4 | 12,873 | 14.9 | <0.001 |
| Hyperlipidemia | 160 | 21.5 | 6287 | 16.3 | 6447 | 16.4 | 6664 | 7.72 | <0.001 |
| Dementia | 2 | 0.27 | 151 | 0.39 | 153 | 0.39 | 236 | 0.27 | <0.001 |
| Parkinsonism | 7 | 0.94 | 389 | 1.01 | 396 | 1.01 | 424 | 0.49 | <0.001 |
| Trigeminal neuralgia | 2 | 0.27 | 55 | 0.14 | 57 | 0.14 | 54 | 0.06 | <0.001 |
| Temporomandibular joint disorders | 4 | 0.54 | 194 | 0.50 | 198 | 0.50 | 173 | 0.20 | <0.001 |
| Anxiety | 27 | 3.63 | 1541 | 3.99 | 1568 | 3.99 | 370 | 0.43 | <0.001 |
| Depression | 45 | 6.05 | 1994 | 6.17 | 2039 | 5.18 | 436 | 0.51 | <0.001 |

Chi-square test compared with total SD.
[a] *t*-Test.

95% CI = 1.39–2.24) (Table 2). By contrast, the risk of BMS was higher in male nonapnea SD patients (IRR = 3.50, 95% CI = 3.28–3.73) than in female patients. For age stratification, the risk of BMS was highest in apnea SD patients aged >65 years (IRR = 3.67, 95% CI = 2.64–5.10), and in nonapnea SD patients aged ≤40 years (IRR = 3.34, 95% CI = 3.10–3.61). Table 2 lists the adjusted HRs of BMS according to various age groups. Compared with patients younger than 40 years of age, the HR increased with increased age in the apnea SD cohort and in the nonapnea SD cohort.

Table 3 presents the IRRs of BMS classified according to comorbidities. In the non-comorbid subgroup without any comorbidities, the risk of BMS was significantly higher in the apnea SD patients (adjusted HR = 2.98, adjusted for age and gender, 95% CI = 1.11–8.04) and in the nonapnea SD patients (adjusted HR = 3.05, adjusted for age and gender, 95% CI = 2.57–3.63) than the non-SD cohort. Apnea SD patients without comorbidity generally had a higher IRR of BMS development than non-SD patients. This association was similar for the risk of BMS among the nonapnea SD cohort. Table 3 presents the relationships among apnea SD patients with comorbidity, such as hypertension (IRR = 3.56, 95% CI = 2.78–4.57), hyperlipidemia (IRR = 3.13, 95% CI = 2.30–4.26), anxiety (IRR = 5.04, 95% CI = 2.48–10.3) or depression (IRR = 17.5, 95% CI = 10.2–29.9), compared with non-SD cohort with comorbidities. In the nonapnea SD cohort, patients with diabetes, hypertension, hyperlipidemia, trigeminal neuralgia, anxiety or depression was also associated with higher risk of BMS than non-SD cohort with those comorbidities. Anxiety (adjusted HR = 3.29; 95% CI = 1.53–7.09) remained significant factors of an increased risk of BMS development in the apnea SD cohort and non-SD cohort after adjusting for age, sex, and other comorbidities. After adjusting for age, sex, and other comorbidities by multivariable Cox model, the risk factors of trigeminal neuralgia (adjusted HR = 5.29, 95% CI = 2.35–11.9), anxiety (adjusted HR = 1.76, 95% CI = 1.26–2.45), and depression (adjusted HR = 1.41, 95% CI = 1.03–1.95) were increased risk of BMS in the nonapnea SD and non-SD cohorts.

## 4. Discussion

BMS has multiple etiological causes and is associated with chronic pain, and psychiatric disorders, such as depression and anxiety. Our study revealed that nonapnea SD and apnea are risk factors of BMS and increased HR in the anxiety and depression comorbidity group in both apnea and nonapnea SD group.

In this study, SD was classified into apnea and nonapnea SD group because apnea SD (obstructive sleep apnea syndrome, OSAS) is an organic disorder with a hypoxemia mechanism affecting

**Table 2**
Comparison of incidence densities and hazard ratio of burning mouth syndrome in study subjects.

| | Control | | Apnea SD | | IRR[b] (95% CI) | Adjusted HR[c] | Non-apnea SD | | IRR[b] (95% CI) | Adjusted HR[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Rate[a] | Case | Rate[a] | | (95% CI) | Case | Rate[a] | | (95% CI) |
| All | 345 | 4.19 | 9 | 11.9 | 2.84 (2.45, 3.30)** | 2.56 (1.30, 5.05)** | 490 | 12.8 | 3.07 (2.95,3.19)*** | 2.89 (2.51, 3.34)*** |
| Gender | | | | | | | | | | |
| Female | 238 | 4.49 | 6 | 20.8 | 4.63 (3.82,5.61)*** | 1.27 (1.01, 1.59)* | 323 | 12.9 | 2.87 (2.74,3.01)*** | 1.11 (0.96, 1.29) |
| Men | 107 | 3.63 | 3 | 6.41 | 1.76 (1.39,2.24)*** | 1 (Reference) | 167 | 12.7 | 3.50 (3.28,3.73)*** | 1 (Reference) |
| Age | | | | | | | | | | |
| ≤40 | 57 | 2.45 | 1 | 3.96 | 1.62 (1.13, 2.31)** | 1 (Reference) | 96 | 8.19 | 3.34 (3.10,3.61)*** | 1 (Reference) |
| 41–65 | 207 | 4.66 | 6 | 14.8 | 3.18 (2.61,3.88)*** | 1.85 (1.38, 2.48)*** | 275 | 13.9 | 2.97 (2.82,3.13)*** | 1.72 (1.43, 2.07)*** |
| >65 | 81 | 5.48 | 2 | 20.1 | 3.67 (2.64,5.10)*** | 2.16 (1.51, 3.09)*** | 119 | 18.1 | 3.29 (3.03,3.58)*** | 2.16 (1.72, 2.71)*** |

[a] Rate, incidence rate, per 10,000 person-years.
[b] IRR, incidence rate ratio.
[c] Adjusted HR: mutually adjusted for age, gender, diabetes, hypertension, hyperlipidemia, dementia, parkinsonism, trigeminal neuralgia, temporomandibular joint disorders, anxiety and depression in Cox proportional hazards regression model.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

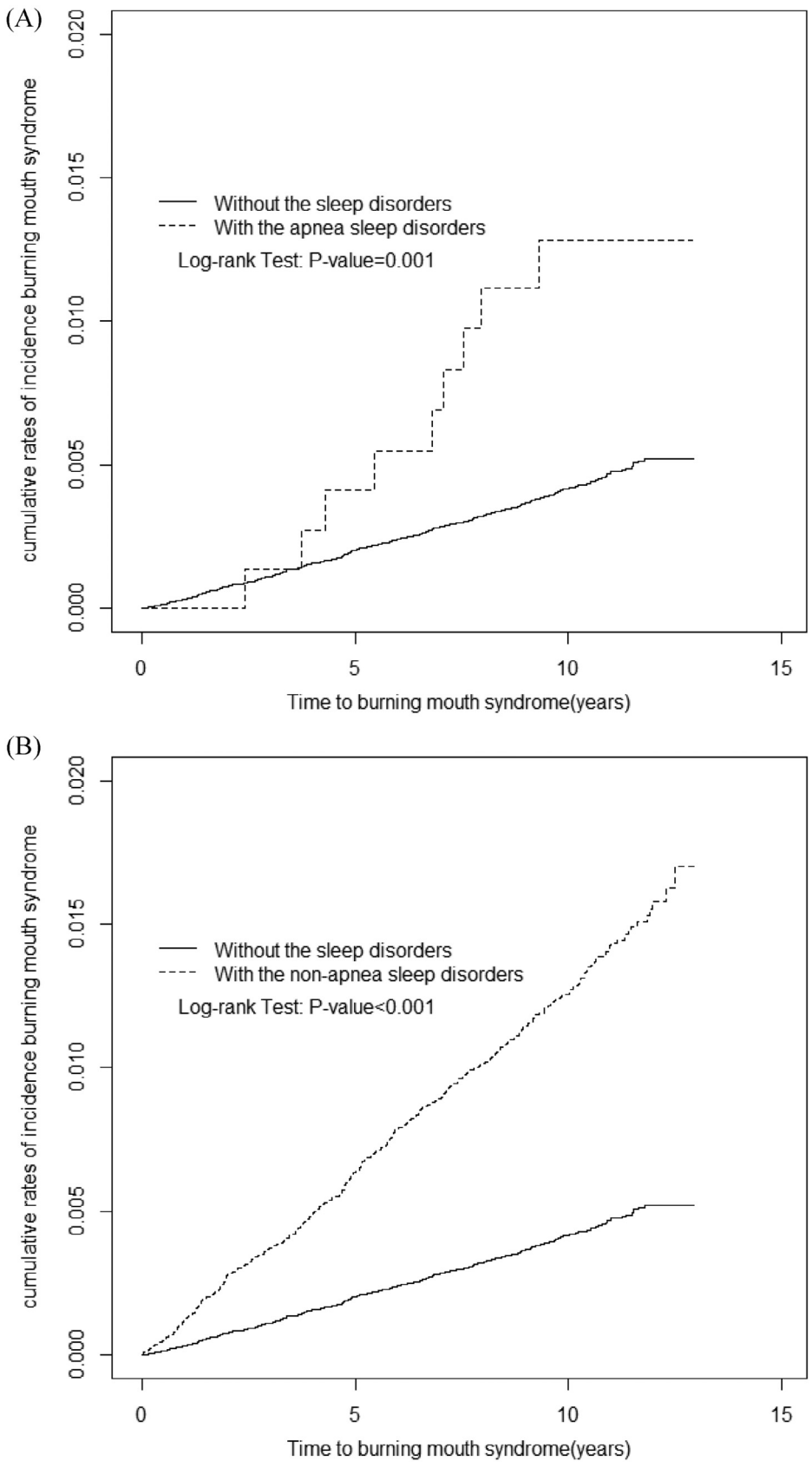


**Fig. 1.** Cumulative incidence of burning mouth syndrome compared between two cohorts: (A) with apnea SD and without SD and (B) with non-apnea SD and without SD.

**Table 3**
Incidence of BMS by comorbidity and Cox model measured hazards ratio for patients with SD compared with those without SD.

| | Control | | Apnea SD | | IRR[b] (95% CI) | Adjusted HR[c] | Non-apnea SD | | IRR[b] (95% CI) | Adjusted HR[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Case | Rate[a] | Case | Rate[a] | | (95% CI) | Case | Rate[a] | | (95% CI) |
| None[d] | 258 | 3.89 | 4 | 9.57 | 2.46 (1.98, 3.06)*** | 2.98 (1.11, 8.04)*** | 261 | 11.3 | 2.91 (2.77, 3.03)*** | 3.05 (2.57, 3.63)*** |
| Diabetes | | | | | | | | | | |
| No | 335 | 4.18 | 9 | 12.5 | 2.98 (2.56, 3.47)*** | 1 (Reference) | 458 | 12.6 | 3.02 (2.90, 3.14)*** | 1 (Reference) |
| Yes | 10 | 4.21 | 0 | 0.00 | – | 0.71 (0.37, 1.36) | 32 | 16.9 | 4.02 (3.24, 4.98)*** | 0.98 (0.71, 1.35) |
| Hypertension | | | | | | | | | | |
| No | 283 | 3.98 | 5 | 9.06 | 2.28 (1.87, 2.77)*** | 1(Reference) | 352 | 12.2 | 3.06(2.94, 3.20)*** | 1 (Reference) |
| Yes | 62 | 5.47 | 4 | 19.5 | 3.56 (2.78, 4.57)*** | 1.06 (0.79, 1.43) | 138 | 14.8 | 2.71 (2.47, 2.97)*** | 0.95 (0.80, 1.14) |
| Hyperlipidemia | | | | | | | | | | |
| No | 307 | 4.04 | 6 | 10.1 | 2.50 (2.08, 2.99)*** | 1 (Reference) | 384 | 12.0 | 2.98 (2.87, 3.11)*** | 1 (Reference) |
| Yes | 38 | 5.93 | 3 | 18.6 | 3.13 (2.30, 4.26)*** | 1.25 (0.88, 1.77) | 106 | 16.9 | 2.84 (2.50, 3.23)*** | 1.21 (0.99, 1.46) |
| Dementia | | | | | | | | | | |
| No | 344 | 4.18 | 9 | 11.9 | 2.85 (2.45, 3.31)*** | 1 (Reference) | 489 | 12.8 | 3.07 (2.96, 3.19)*** | 1 (Reference) |
| Yes | 1 | 8.39 | 0 | 0.00 | – | 1.04 (0.14, 7.61) | 1 | 10.7 | 1.27 (0.63, 2.57) | 0.81 (0.20, 3.27) |
| Parkinsonism | | | | | | | | | | |
| No | 341 | 4.15 | 9 | 12 | 2.89 (2.49, 3.36)*** | 1 (Reference) | 484 | 12.8 | 3.08 (2.96, 3.20)*** | 1 (Reference) |
| Yes | 4 | 15.6 | 0 | 0.00 | – | 2.54 (0.93, 6.98) | 6 | 19.3 | 1.23 (0.77, 1.96) | 1.54 (0.81, 2.89) |
| Trigeminal neuralgia | | | | | | | | | | |
| No | 344 | 4.18 | 9 | 11.9 | 2.86 (2.46, 3.32)*** | 1 (Reference) | 485 | 12.7 | 3.05 (2.93, 3.17)*** | 1 (Reference) |
| Yes | 1 | 21.3 | 0 | 0.00 | – | 3.66 (0.51, 26.2) | 5 | 100.7 | 4.73 (1.12, 20.1)* | 5.29 (2.35, 11.9)*** |
| Temporomandibular joint disorders | | | | | | | | | | |
| No | 345 | 4.19 | 9 | 12.0 | 2.86 (2.45, 3.31)*** | 1 (Reference) | 484 | 12.7 | 3.04 (2.92, 3.16)*** | 1 (Reference) |
| Yes | 0 | 0.00 | 0 | 0.00 | – | – | 6 | 31.1 | – | 1.58 (0.70, 3.55) |
| Anxiety | | | | | | | | | | |
| No | 340 | 4.14 | 7 | 9.58 | 2.31 (1.96, 2.74)*** | 1 (Reference) | 456 | 12.4 | 3.00 (2.89, 3.12)*** | 1 (Reference) |
| Yes | 5 | 15.1 | 2 | 76.2 | 5.04 (2.48, 10.3)*** | 3.29 (1.53, 7.09)** | 34 | 23.2 | 1.54 (1.01, 2.34)* | 1.76 (1.26, 2.45)*** |
| Depression | | | | | | | | | | |
| No | 343 | 4.18 | 5 | 7.00 | 1.67 (1.37, 2.04)*** | 1 (Reference) | 451 | 12.5 | 2.98 (2.87, 3.10)*** | 1 (Reference) |
| Yes | 2 | 5.45 | 4 | 95.2 | 17.5 (10.2, 29.9)*** | 2.23 (0.97, 5.13) | 39 | 20.0 | 3.67 (2.07, 6.50)*** | 1.41 (1.02, 1.95)* |

[a] Rate, incidence rate, per 10,000 person-years.
[b] IRR, incidence rate ratio.
[c] Adjusted HR: mutually adjusted for age, gender, diabetes, hypertension, hyperlipidemia, dementia, parkinsonism, trigeminal neuralgia, temporomandibular joint disorders, anxiety and depression in Cox proportional hazards regression model.
[d] Adjusted for age and gender.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

respiratory ventilation [25]. However, nonapnea SD might alter the immune system and induce a systemic inflammation condition. Previous studies have reported that sleep deprivation can elevate the levels of proinflammation cytokines including CRP, IL-6, and TNF-a [26,27]. Studies have also shown that SD can alter the immune system which, mediated by the augmented activity of the hypothalamic-pituitary-adrenal axis (HPA) and stress, is considered one of the major triggers of insomnia [28,29]. It has been suggested that SDs exert mutual effects with BMS through pain and the neuropathic interaction pathway which might be related to the HPA stress pathway or immune mediators related to the pain pathway mechanism. Our findings also suggest that female patients with an apnea disorder have a higher risk than do male patients, which is consistent with the etiology of BMS [13]. The age incidence of our findings being dominant above 41 years, neither in apnea SD nor nonapnea disorder groups, infers that BMS typically develops in middle-age patients with SD. In this study, the comorbidity-specific incidence was higher in nonapnea SD with trigeminal neuralgia in BMS patients, implying that BMS is linked with neuropathic disorder and pain [19,30,31]. Our findings are also consistent with these studies.

The strength of our study includes its use of population-based data that are highly representative of the general population. However, certain limitations to our findings should be considered. First, the NHIRD does not contain detailed information regarding smoking habits, alcohol consumption, socioeconomic status, and family history of systemic diseases, all of which might be risk factors for SD or BMS. Second, the evidence derived from a retrospective cohort study is generally lower in statistical quality than that from randomized trials because of potential biases related to adjustments for confounding variables. Despite our meticulous study design and control measures for confounding factors, bias resulting from unknown confounders might have affected our results. Third, all data in the NHIRD are anonymous. Thus, relevant clinical variables, such as blood pressure, imaging results, pathology findings, and serum laboratory data were unavailable regarding our study-patient cases. However, the data regarding SD or BMS diagnoses were nonetheless reliable.

## 5. Conclusion

This population-based retrospective cohort study determined that patients with SD have an increased risk of BMS. This implies that management of SD can improve BMS symptoms by eliminating systemic inflammatory cytokines, reduce stress process, and/or modulating pain sensation. Good quality of sleep might improve the progress of BMS. The underlying mechanism remains unclear, and adequate, high quality sleep might eliminate the risk factors of BMS. This paper could also provide therapeutic hints for clinicians. However, additional large-scale studies are necessary to confirm these findings.

## Conflict of interest

The authors have declared that no competing interests exist.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.06.009.

## Author contributions

**Conceived and designed the experiments:** Chun-Feng Lee, Chia-Hung Kao.

**Performed the experiments:** Chun-Feng Lee, Cheng-Li Lin, Chia-Hung Kao.

**Analyzed the data:** Chun-Feng Lee, Cheng-Li Lin, Chia-Hung Kao.

**Contributed reagents/materials/analysis tools:** Chia-Hung Kao.

**Wrote the manuscript:** All authors.

**Approval of the manuscript:** All authors.

## Acknowledgment

The study was supported in part by the study projects (DMR-103-018 and DMR-103-020) in China Medical University Hospital, Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW103-TDU-B-212-113002), Health and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW103-TD-B-111-03, Taiwan). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## References

[1] Taiwan Society of Sleep Medicine website: <http://www.tssm.org.tw/index.php> [accessed 12.03.18].
[2] Sleep disorders and sleep deprivation: an unmet public health problem. Washington DC: National Academy of Sciences; 2006.
[3] Coren S. Sleep health and its assessment and management in physical therapy practice: the evidence. Physiother Theory Pract 2009;25:442–52.
[4] Chokroverty S. Overview of sleep & sleep disorders. Indian J Med Res 2010;126–40.
[5] Lashley FR. A review of sleep in selected immune and autoimmune disorders. Holist Nurs Pract 2003;17:65–80.
[6] Sanjai R, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep duration and biomarkers of inflammation. Sleep 2009;32:200–4.
[7] Palma BD, Tiba PA, Machado RB, Tufik S, Suchecki Dl. Immune outcomes of sleep disorders: the hypothalamic-pituitary-adrenal axis as a modulatory factor. Rev Bras Psiquiatr 2007;29(Suppl.):S33–8.
[8] Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Med Rev 2006;10:357–69.
[9] Onen SH, Alloui A, Gross A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res 2001;10:35–42.
[10] Jennum P, Drewes AM, Andreasen A, Nielsen KD. Sleep and other symptoms in primary fibromyalgia and in healthy controls. J Rheumatol 1993;20:1756–9.
[11] Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavior clinical trials literature. Sleep Med Rev 2004;8:119–32.
[12] Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E, Dell'Aversana G, Mignogna MD. Sleep disturbance in patients with burning mouth syndrome: a case control study. J Orofac Pain 2013;27:304–13.
[13] Gurvits GE, Tan A. Burning mouth syndrome. World J Gastro-enterol 2013;19:665–72.
[14] Klasser GD, Fischer DJ, Epstein JB. Burning mouth syndrome: recognition, understanding, and management. Oral Maxillofacial Surg Clin N Am 2008;20:255–71.
[15] Mersky H, Bogduk N. Descriptions of chronic pain syndromes and definitions of pain terms. In: Classification of chronic pain. 2nd ed. Seattle, WA: IASP Press; 1994. p. 74.
[16] Netto FO, Diniz IM, Grossmann SM, de Abreu MH, do Carmo MA, Aguiar MC. Risk factors in burning mouth syndrome: a case-control study based on patient records. Clin Oral Investig 2011;15:571–5.
[17] Grinspan D, Fernandez Blanco G, Allevato MA, Stengel FM. Burning mouth syndrome. Int J Dermatol 1995;34:483–7.
[18] Gilpin SF. Glossodynia. JMMA 1936;106:1722–4.
[19] Forssell H, Jaaskelainen S, Tenovuo O, Hinkka S. Sensory dysfunction in burning mouth syndrome. Pain 2002;99:41–7.
[20] Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332–7.
[21] Grushka M, Sessle BJ, Howly TP. Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. Pain 1987;28:169–84.
[22] Rojo L, Silvestre FJ, Bagan JV, De Vicente T. Prevalence of psychopathology in burning mouth syndrome. A comparative study among patients with and without psychiatric disorders and controls. Oral Surg Oral Med Oral Pathol 1994;78:312–16.
[23] de Souza FT, Teixeira AL, Amaral TM, dos Santos TP, Abreu MH, Silva TA, et al. Psychiatric disorders in burning mouth syndrome. J Psychosom Res 2012;72:142–6.
[24] Chainani-Wu N, Madden E, Silverman S Jr. A case-control study of burning mouth syndrome and sleep dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:203–8.
[25] Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. Sleep 2007;30:291–303.
[26] Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol 2004;43:678–83.
[27] Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. J Allergy Clin Immunol 2001;107:165–70.
[28] Palma BD, Tiba PA, Machado RB, Tufik S, Suchecki D. Immune outcomes of sleep disorders: the hypothalamicpituitary-adrenal axis as a modulatory factor (in Portuguese). Rev Bras Psiquiatr 2007;29(Suppl. 1):S33–8.
[29] Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. J Clin Endocrinol Metab 2005;90:3106–14.
[30] Komiyama O, Obara R, Uchida T, Nishimura H, Iida T, Okubo M, et al. Pain intensity and psychosocial characteristics of patients with burning mouth syndrome and trigeminal neuralgia. J Oral Sci 2012;54:321–7.
[31] Siviero M, Teixeira MJ, de Siqueira JT, Siqueira SR. Somesthetic gustatory, olfactory function and salivary flow in patients with neuropathic trigeminal pain. Oral Dis 2010;16:482–7.